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Letter to the Editor

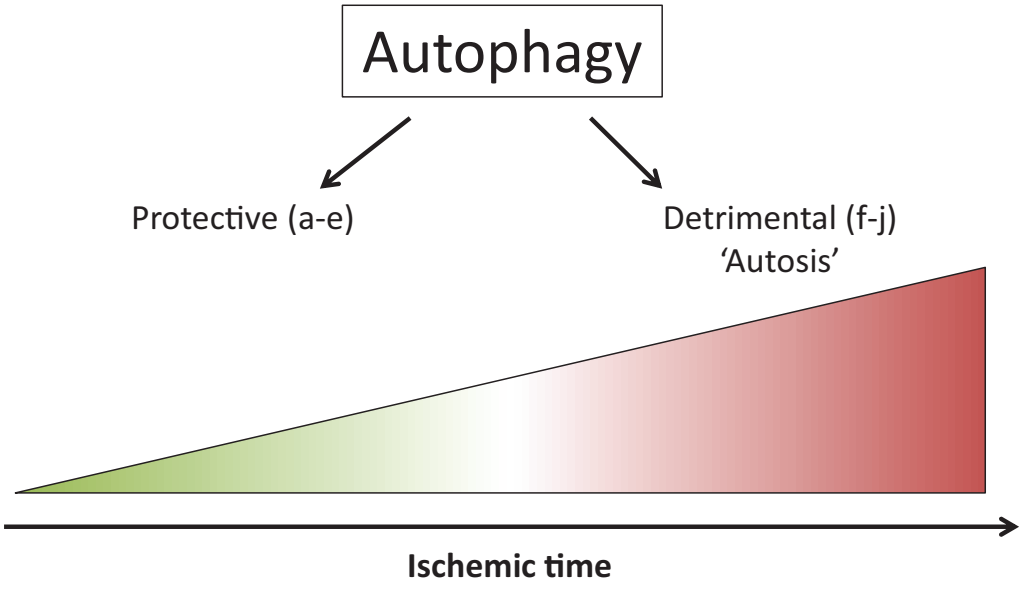
Autophagy in Renal Ischemia-Reperfusion Injury: Friend or Foe?

To the Editor:

The recent review on autophagy by Pallet et al published in the *Journal* addresses the interesting possibility to promote autophagy to limit ischemia-reperfusion injury (IRI) and reduce delayed graft function after kidney transplantation (1). Indeed, autophagy is generally regarded as a protective response to various types of pathological injuries—among them renal IRI—and its stimulation may therefore improve graft outcome.

Pallet et al (1) judiciously notice that certain well-known stimulators of autophagy, such as rapamycin (mTOR inhibitor), paradoxically aggravate IRI. They attribute this discrepancy to the fact that mTOR inhibitors not only stimulate autophagy but also inhibit cell growth, essential for kidney recovery after injury. For this reason, Pallet et al (1) propose to evaluate a more selective autophagy stimulator: the cell-permeable peptide Tat-Beclin 1.

With this letter we want to highlight that stimulation of autophagy may not necessarily protect the graft. Indeed, Liu et al (2) recently demonstrated the existence of autophagy-dependent cell death in various cell lines and a pathological model of cerebral ischemia. This process, termed ''autosis,'' is triggered by high levels of autophagy



Publication	Ischemia	Publication	Ischemia
(a) Liu S Autophagy 2012: 8(5)	25 min	(f) Nakagawa S Eur J Pharmacol 2012: 696(1-3)	40 min
(b) Jiang M Kidney Int 2012: 82(12)	25 min	(g) Chien CT Transplantation 2007: 84(9)	45 min
(c) Jiang M Am J Pathol 2010: 176(3)	30 min	(h) Isaka Y Transplant Proc 2009: 41(1)	45 min
(d) Kimura T J Am Soc Nephrol 2011: 22(5)	40 min	(i) Yeh CH Life Sci 2010: 86(3-4)	45 min
(e) Lempiainen J Acta Physiol 2013: 208(4)	40 min	(j) Wu HH J Biomed Sci 2009: 16(1)	60 min

Figure 1: Proposed model. The longer the ischemic time (the ischemic severity), the greater the chance of excessive detrimental autophagy or autosis, as suggested by analysis of the different publications, summarized in the table below the scheme. Protective autophagy was found in models with 25–40 min of ischemia (a–e), detrimental autophagy was observed upon 40–60 min of ischemia (f–j).

(2) and was induced by the autophagy stimulator Tat-Beclin 1 that Pallet et al (1) are considering to evaluate in the protection of kidney grafts from IRI.

We hypothesize that autophagy may have both protective *and* detrimental effects depending on the severity of ischemia, the degree of autophagy activation, the phase of IRI and probably other still unknown factors. This concept of a dual effect of autophagy is supported by the findings of all the reports on *in vivo* autophagy modulation in renal IRI; autophagy was protective when ischemia time was short (20–40 min), but detrimental after more prolonged ischemia (40–60 min) (Figure 1). More severe ischemia could increase the likelihood of high levels of autophagy leading to cell death, as described by Liu et al (2). Ischemia of 40 min likely represents the ''fatal'' turning point above which autophagy transforms from a cell survival into a cell death pathway in the examined models, but the turning point will likely vary according to the species, strain, gender and the type (warm or cold) and length of ischemia in the studied model.

Consequently, it is essential to unravel the characteristics of autophagy in renal IRI and the factors influencing them. Beyond that, other transplant-related injuries (hypoxia and surgical manipulation in donors and recipients, cold preservation, drug toxicity, etc.) likely also affect autophagy as it is a ubiquitous cell adaptation process. Finally, autophagy likely also plays a role in graft rejection since it regulates innate and adaptive immune cells. We agree with Pallet et al (1) that modulating autophagy represents a new avenue to protect kidney grafts from IRI that needs to be explored. However, the complexity and the multitude of the transplant-related events influencing autophagy, the probably ambivalent (protective and detrimental) characteristics of autophagy and the involvement of multiple cell compartments (parenchymal and nonparenchymal) may make this strategy very challenging.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

References

1. Pallet N, Livingston M, Dong Z. Emerging functions of autophagy in kidney transplantation. Am J Transplant 2014; 14: 13–20.
2. Liu Y, Shoji-Kawata S, Sumpter RM Jr, et al. Autosis is a Na^+, K^+-ATPase-regulated form of cell death triggered by autophagy-inducing peptides, starvation, and hypoxia-ischemia. Proc Natl Acad Sci USA 2013; 110: 20364–20371.